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13. SUPPLEMENTARY NOTES				
14. ABSTRACT This project has developed magnetic resonance (MR) imaging approaches to estimate severity of tissue damage after spinal cord injury (SCI). We have performed q-space imaging (QSI) in small animal spinal cord models with high field research imagers and in pig spinal cord specimens using clinical human instruments. We have shown that QSI permits precise estimates of axonal diameter distributions. We have developed direct imaging of spinal cord myelin using ultra short TE (UTE) and zero TE (ZTE) methods that take advantage of the extremely short T2 of myelin. We have shown these methods to be quantitatively reliable. We have developed a high b-value imaging method that permits estimates of axon diameters in spinal cord and applied this to human subjects. We have developed inhomogeneous magnetization transfer (IHMT) approaches to estimating spinal cord myelin content and applied this to normal volunteers. The results appear consistent with the know distribution of myelin in normal spinal cord. Overall, we have developed a suite of approaches to spinal cord imaging that permit estimation of axonal loss and myelin loss as a result of SCI. These methods will permit better characterization of tissue injury in SCI, selection of therapies and evaluation of treatment effects.				
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INTRODUCTION

Spinal cord injury can devastate lives, cause severe permanent disability, and early death. Although there are promising many avenues of investigation, a common challenge is determining the exact nature of the tissue damage sustained. The cord deteriorates after injury, and there are no reliable methods to predict the histological details. Yet, this information would be critical in selecting therapies and evaluating their effects on the intended targets. Limited success of a treatment could be due to applying it inappropriately. We seek to improve tissue characterization thus permitting better selection of potential therapy and better evaluation of treatment efficacy.

BODY

The overall goals of this project have been to use magnetic resonance (MR) of the spinal cord to infer damage to axons and to estimate myelin loss. We have made progress on these goals, with some limitations as described below.

A major goal has been to advance diffusion MR imaging of the cord. This involved improved techniques for diffusion acquisition that would permit estimates of axonal density and diameter. An emerging approach for these studies has been q-space imaging (QSI). We have shown that this produces remarkably precise predictions of axonal diameter distributions when applied to fixed rat spinal cords and validated with microscopy. However, scaling this up to imaging live human subjects poses a number of technical problems that were a subject of our research. QSI typically relies on high q values, which are difficult to achieve in vivo. Part of our work focused on creating extremely high b value techniques that would permit direct assessment of axonal diameter as well as implementation of QSI.

We succeeded in obtaining high b value cross sectional imaging of human volunteer spinal cords and showed that these images reproduce reported axonal diameter distributions. Of course, we cannot directly validate these inferences with human subjects, as there are essentially no conditions what would require resection of the spinal cord to produce histological confirmation.

We have continued to pursue histological validation in pig spinal cords (similar in scale to human) using a human clinical imaging instrument. Our data continue to support the reliability of these estimates. This work thus encourages us to believe that we can use these insights to apply QSI to human subjects and derive valuable predictions of axonal density and diameter.

Another major goal has been inferring myelin loss after SCI. This is a prominent feature of injured cords. The loss of myelin severely impairs conduction velocity. Loss of oligodendrocytes also removes trophic support from the axons. Efforts at repair and regeneration involve, in part, attempts to restore normal spinal cord architecture, including remyelination. Currently there are no methods available to estimate myelin loss in human subjects. We have pursued two unrelated MR approaches to quantitating myelin.

The first directly visualizes myelin by creating images with extremely short TE values. These capture the short T2 signal of myelin, which is not detectable with conventional imaging. Using this approach, we have shown high quantitative accuracy in rat spinal cord specimens using a high field research instrument. Our goal of extending this work to human imaging has suffered technical and personnel problems as discussed below. We remain enthusiastic about the prospects for applying this work to human subjects, but substantial further technical development will be required.

The other approach to imaging spinal cord myelin has been applied in brain and spinal cord imaging in human subjects. This method relies on a feature of the magnetization transfer (MT) phenomenon. Specifically, it is possible to assess an asymmetry in MT, termed inhomogeneous magnetization transfer (IHMT) that appears unique to myelin. This approach has shown high association with known distribution of myelin and it appears to produce valuable estimates of myelin content. We have not, as yet, validated the myelin estimates in animal models, but such studies are in the planning stages.

Thus, we have a method for myelin imaging that has shown high accuracy, validated in small animal spinal cord specimens and confirmed by biochemical determination of myelin content. This method will require substantial technical development to implement in human subjects, but if successful, it will permit direct visualization of in vivo myelin content. We have a second method that is readily performed in human subjects, but that awaits histological validation in animal models.

Between these two approaches, we believe we have made substantial progress on the second goal of assessing myelin content.

Limitations- The University of Pennsylvania site has been hampered by equipment problems. An upgrade of the high field MR imaging equipment, which ultimately will improve the capabilities of the instrument, created major delays. The new scanner required completely new pulse sequences and hardware upgrades to restore the ability to use a custom-built gradient coil. This coil, designed and fabricated in-house, permitted far higher imaging resolution and gradient stability than off the shelf alternatives. However, the incompatibility of the coil and software with the new instrument introduced severe delays in completing the goals of the high field imaging of small animal spinal cords- a key feature of the work at UPenn.

The Beth Israel Deaconess Medical Center (BIDMC) site also experienced delays, in this case due to personnel turnover. A postdoctoral fellow who worked quite productively on the IHMT and high b-value imaging left due to family reasons, creating major delays in carrying with work forward. However, both components of the project showed substantial progress.

KEY RESEARCH ACCOMPLISHMENTS

- Implemented animal models of spinal cord injury.
- Demonstrated direct imaging of myelin using ultra short TE and zero TE techniques.
- Demonstrated the quantitative accuracy of these myelin measures.
- Performed QSI on small animal spinal cord specimens.
- Generated preliminary data on QSI imaging of pig spinal cords on a human clinical MR instrument.
- Implemented upgrades to the Bruker small bore high field MR instrument permitting use of a custom built spinal cord coil.
- Developed high b-value imaging of the human spinal cord in volunteers.
- Demonstrated axonal diameter distribution correlates of cross sectional imaging in human spinal cord in vivo.
- Applied IHMT to spinal cord imaging in human subjects.
- Documented high IHMT in spinal cord white matter, correlating with myelin content and low values in grey matter.

REPORTABLE OUTCOMES

- High spatial resolution spinal cord QSI for estimation of axonal diameter distribution.
- Quantitative direct myelin imaging in spinal cord.
- High b-value spinal cord imaging in human subjects correlates with axonal diameters.
- IHMT imaging in human subjects correlates with myelin content.

CONCLUSION

This work has advanced imaging capabilities of normal and injured spinal cord. Principles have been validated in animal models and approaches have been implemented for human subjects.

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